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PEDIATRIC NEWS

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CHIEF'S CORNER

Rheumatology Service

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The adult rheumatology section of the Internal Medicine Department sponsors a pediatric rheumatology consultative service at Wilford Hall Medical Center (WHMC). Our staff consists of three board certified adult rheumatologists. While we are not board eligible or certified in pediatric rheumatology, we have had pediatric rheumatology experience as part of our adult rheumatology training. This service is provided under a working arrangement between the Department of Rheumatology and the Department of Pediatric at WHMC. The following statements describe our working arrangements:

1. The department of Rheumatology sponsors a one half day per month pediatric rheumatology clinic in which 8-10 patients are evaluated or followed-up.
2. This clinic takes place in the adult rheumatology clinic area every second Thursday of the month.
3. The department of pediatrics provides a staff general pediatrician for each monthly clinic. This pediatrician will ensure that our recommendations are followed or that a second opinion is obtained from a pediatric rheumatology when necessary.
4. All patients seen in our clinic must have a primary pediatrician, since we are adult rheumatologists without formal pediatric training.
5. Inpatient consultative service is provided on a daily basis as necessary.

Usually, our initial evaluation takes about two hours. The reason for this is that cases are presented to all members of the department, where we discuss the best treatment plans and advances in the field of pediatric rheumatology. Occasionally, parents prefer to have their child seen by a formally trained Pediatric Rheumatologist and not an adult one. In that situation, we recommend that the referring pediatrician fill out a DD Form 2161 (referral for civilian medical care). While there are no board certified pediatric rheumatologists in the San Antonio area, there are several in both the Houston and Dallas-Fort Worth areas.

Among our referral patients, the most common diagnoses include Juvenile Chronic Arthritis, and Systemic Lupus Erythematosus, but we follow a group of children with a variety of uncommon conditions such as polyarteritis nodosa, scleroderma, and dermatomyositis. We also provide a Disease Modifying Antirheumatic Drug Clinic. This clinic provides education and monitoring for all antirheumatic drugs approved for treatment of children with rheumatological problems like, non-steroidal anti-inflammatory agents, steroids, gold, penicillamine, plaquenil, methotrexate, azulfidine, and Tumor Necrosis Factor inhibitors.

Our DoD consultant for pediatric rheumatology is Capt (Dr) Ildy Katona, USN, Chairman of Pediatrics, Uniformed Services University. She can be reach at USHUS, (310) 295-3745.

Fluid & Electrolyte Potpourri:

Dehydration: the Dreaded “D”
word- what does it mean?
What is new in treating
Hemorrhagic Shock?

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“Dehydration”

Infants and children are often said to be “Dehydrated” by pediatricians. What in fact does this term mean? To physiologists it means that the body has lost water from its body fluid spaces. Unfortunately pediatricians often confuse “Dehydration” and hypovolemia leading to inaccuracies in diagnosis and therapy. It is critical that Pediatricians, above all other physicians, understand the important differences between dehydration & volume depletion. Their patients are small, dependent beings who can experience large changes in their fluid spaces with relatively small imbalances between intake & output. Pediatricians must understand the difference between free water (no Na) and saline and how, abnormalities in the net balance of these different fluids, causes a variety of different clinical disorders. Pediatricians must understand the two main body fluid spaces namely the Intracellular or Free water fluid space & the Extracellular or saline fluid space and how each space is regulated & the clinical consequences of an abnormality in each space.

Basically when Na is added or removed from the body fluids it, & the water it osmotically, attracts (making Saline) is stuck in the ECF space. Thus saline affects the ECF

space but the ICF space volume is not affected. When Free water is added or removed from the body most of it (2/3) comes from or goes to the intracellular fluid space (which is the largest fluid space in the body) and this affects the tonicity of the body fluids and usually the serum Na concentration. Plasma tonicity is determined by solutes, primarily sodium salts, in the extracellular fluid, which determine the transcellular distribution of water. Plasma tonicity is sensed by osmoreceptors & thirst centers in the brain. Abnormalities in tonicity trigger mechanisms to change the intake (thirst) or output (urine concentration or dilution) of free water (table 1). Changes in body fluid tonicity affect CNS function and have CNS signs and symptoms. By comparison, the extracellular fluid volume is determined by the absolute amounts of sodium and water that are present. The extracellular volume is regulated by alterations in renal sodium excretion, which are primarily due to variations in activity of the renin-angiotensin-aldosterone and sympathetic nervous systems and the secretion of atrial natriuretic peptide in response to volume sensors in the atria, renal vasculature & Carotid Sinus. There is no regulation of Na intake (Table 1). Changes in ECF volume affect

with one space increased, normal or decreased and the other space normal, increased or decreased. This is why the term dehydration is meaningless.

Fluid & Electrolyte Definitions

Hyponatremia - reflects an excess of free water. It is always due to an inability to excrete ingested or infused water.

Hypernatremia - reflects a deficit of free water. This can be produced by the administration Salt (salt poisoning) or a hypertonic salt solution such as NaHCO₃. However it is usual due to a lack of replacement of usual or increased free water losses.

Edema - is a condition of saline excess. These patients do not usually develop hypernatremia because stimulation of the release of antidiuretic hormone and thirst will result in the retention of a proportionate amount of water.

Hypovolemia or Decrease ECF space- refers to any condition in which the extracellular fluid volume, especially the plasma component of that space, is reduced and, when severe, leads to a clinically apparent reduction in tissue perfusion due to compromised

cardiac output. It can be produced by salt and water loss from the ECF space (ie vomiting, diarrhea, diuretics)

bleeding, or third spacing. It can be caused by free water loss alone however, since saline loss comes totally from the ECF space whereas pure water loss comes from the total

Differences between Osmoregulation and Volume Regulation		
	Osmoregulation	Volume regulation
What is being sensed	Plasma osmolality	Effective circulating volume
Sensors	Hypothalamic osmoreceptors	Carotid sinus Afferent glomerular arteriole Atria
Effectors	Antidiuretic hormone	Sympathetic nervous system Renin-angiotensin-aldosterone Natriuretic peptides Pressure natriuresis Antidiuretic hormone
What is affected	Water excretion (via ADH) Water intake (via thirst)	Sodium excretion

cardiac output if decreased and cause edema if increased. Thus a pediatrician’s patients can have simultaneous abnormalities of their patients Saline & Free water spaces

body water of which only about 1/3 is ECF Space, to produce the same degree of extracellular volume depletion 3 times as much free water must be lost as saline. The loss of this free water would cause severe hypernatremia in addition to the hypovolemia.

Thus it can be seen that the clinical distinction between saline loss and pure water loss may be made by measurement of the plasma sodium concentration. Patients with pure free water deficits are always hypernatremic & in fact the amount of free water lost from the total body water is proportional to the % change in the serum Na concentration. Patients with pure saline loss have a plasma sodium concentration that is normal. Hypernatremia can occur with salt and water loss if water is lost in excess of salt. Such patients may be considered to have both a free water deficit and a saline deficit and have impairment in both plasma tonicity and volume. The clinician can only assess the status of the Saline or ECF space by a clinical evaluation. Excess saline is indicated by edema &/or weight gain. A decrease in the ECF space is determined by a careful history & physical exam. The history is aimed at detecting evidence of loss of Extracellular type fluid (blood or salt water) while the physical exam is aimed at detecting evidence of decreased cardiac output from decreased preload or cardiac output that is maintained by compensatory mechanisms such as tachycardia. The severity of findings in this clinical evaluation can give the clinician a clue as to how much Saline the patient has lost from his ECF space as illustrated in the Table 2.

Once the clinician knows the deficits of excesses in his patient's free water & saline space he can design a rational fluid plan. Since they affect cardiac output, Saline deficits should be restored aggres-

sively (see below for exceptions) with boluses for severe deficits (shock) & complete correction should be accomplished within 16-24 hours. Edema only needs to be treated if causing a clinically significant problem. Free water deficits (hypernatremia) & excesses (hyponatremia) must be corrected slowly over 2-3 days (unless they are acute and causing severe symptoms). Rapid correction in these circumstances can cause severe clinical problems.

What is new in the treatment of Hemorrhagic Shock

Timing of Fluid Resuscitation in Traumatic Shock

For many years, the preoperative approach to hypotensive patients with trauma has included prompt intravenous infusion or isotonic crystalloid solution in order to restore normal blood pressure as quickly as possible. Several clinical and laboratory studies supporting these guidelines showed the reversal of hemorrhagic shock when 2-3 times the volume of blood lost was replaced using crystalloid solution²⁸ However, blood loss in the trauma victim occurs as the result of injury to blood vessels or solid

organs, not from withdrawal of blood through a catheter which was the model used in early studies of hemorrhagic shock. The potential hazards of aggressive crystalloid resuscitation before the hemorrhage from damaged blood vessels is surgically controlled include:

1] Possible negative impact of fluid resuscitation on early clot formation:

2] Possible mechanical disruption of blood clot from a vessel by rapid volume resuscitation

3] The dilution of clotting factors by crystalloid resuscitation increasing the risk of hemorrhage

4.] The risk of a progressive hemodilution decreasing oxygen carrying capacity

In several recent studies there was an apparent improvement in survival for animals only partially resuscitated from uncontrolled hemorrhage compared to animals who received standard aggressive fluid resuscitation.^{28,31} On the basis of these studies, a change in trauma resuscitation for patients sustaining a penetrating torso injury may be indicated especially if there is going to be a delay to surgery since in most studies, re bleeding occurs 30 minutes after aggressive fluid resuscitation. Some have even

Severity of Saline Deficit	MILD	MODERATE	SEVERE
	Saline Deficit as % of BW:		
Infants	5%	10%	15%
Older children	3%	6%	9%
History of Decreased intake	+	++	+++
History of ECF losses	+	++	+++
Thirst	+	++	+++
Skin color	pale	gray	mottled
Temp of extremities	cool	cooler	cold
Dec skin turgor	+	++	+++
Mucous Membranes	dry	very dry	parched
Tears	present	decreased	absent
CNS function	normal	mild changes	ALC
Pulse	+/- inc	inc	very inc
Capillary Refill	2.5 sec	3-4 sec	> 4 sec
Postural Pulse/BP changes	none	mild	severe
Blood Pressure	normal	+/- normal	reduced
Anterior Fontanelle	flat	sl sunken	sunken
Urine output	sl oliguria	olig	marked olig
Urine SpGravity	normal	increased	very increased
Urine Na	normal	low	very low
FeNa	>2%	1-2%	<1%
Hct/Albumin	normal	increased	very increased
BUN	normal	increased	very increased

advocated that the patient should be maintained in a hypotensive state until the bleeding can be stopped surgically. Moderation in the use of intravenous crystalloid, rather than overly aggressive infusion rates to restore BP to normal, now appears to be an acceptable recommendation especially if there is going to be a prolonged delay before definitive surgical control of hemorrhage is achieved.²⁸ However, the issues regarding the acceptance of a blood pressure that is less than normal during a resuscitation remains less clear, and further research is needed to provide definitive recommendations.²⁸

Tailoring of the trauma resuscitation to the individual patients, their pre-existing diseases, the mechanism of injury and the setting in which the patients have been injured and the distance and time they need to be transported to receive definitive surgical care, should still be the accepted form of trauma management. Care providers should remain cautious about applying the principle of "delayed fluid resuscitation" or "hypotensive resuscitation" to all trauma patients, especially those who have sustained blunt trauma and have a possible closed head injury.

References

1. Neilson EG et al. Language guiding therapy: The case of dehydration versus volume depletion 1997; 127:848-853.
2. Watkins SL. The basics of fluid and electrolyte therapy. *Pediatric Annals* 1995; 24:16-22.
3. Avner ED. Clinical disorders of water metabolism: Hyponatremia and hypernatremia. *Pediatric Annals* 1995; 23-30.
4. Angood PB. Timing of trauma resuscitation - Where on the spectrum should it occur? *Trauma Quarterly* 1997;13:251-261.
5. Bickell WH, Wall MJ,

Pepe PE et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331:1105-1109.

6. Shoemaker WC, Peitzman AB, Bellamy R. et al. Resuscitation from severe hemorrhage. *Crit Care Med* 1996;24 (Suppl.):S12-23.

7. Riddez L. Johnson L. Hahn RG. Central and regional hemodynamics during crystalloid fluid therapy after uncontrolled intra-abdominal bleeding. *J Trauma* 1998;44:433-439.

8. Bickell WH. Commentary-timing of trauma resuscitation. *Trauma Quarterly* 1997;13:267-268.

9. Dries DJ. Hypotensive resuscitation. *Shock* 1996;6:311-316.

10. Bickell WH, Brulging SP, Milnamow GA. et al. The detrimental effects of intravenous crystalloid after aortotomy in swine. *Surgery* 1991;110:529.

11. Stern SA. Dronen SL. Birrer P. et al. Effect of blood pressure on hemorrhage volume and survival - in a near-fatal hemorrhage model incorporating a vascular injury. *Ann Emerg Med* 1993;22:155.

12. Owens TM, Watson WC. Prough DS. et al. Limiting initial resuscitation of uncontrolled hemorrhage reduces internal bleeding and subsequent volume requirements. *J Trauma* 1995;39:200-209.



Chronic Headaches in Children

Part II: Treatment

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In the last newsletter I addressed evaluation and diagnosis of a child with headache. This article addresses treatment, emphasizing management of migraine headaches. Table 1 reviews the diagnostic criteria for migraine. Many children fail to meet the criteria due to bilateral pain and lack of pulsating character. Recent large studies have emphasized that children may have a different manifestation of migraine, and that the accepted criteria for "common" migraine developed for adult patients may be too strict to apply to children. Migraines with auras tend to be more readily identified because the aura is so distinctive.

Once symptomatic headache has been excluded, children with recurrent headaches usually fall into two broad groups, those with migraine and those with chronic daily headache. There is a great deal of overlap between these two groups diagnostically, and often the distinction is moot. Most of the medications used to treat acute, severe migraines are useful in other types of headaches, though a few have been developed and studied specifically for migraine (DHE and triptans). Prophylactic agents for migraine are generally useful for other chronic or recurrent headache syndromes that do not strictly meet diagnostic criteria for migraine. Thus the distinction of migraine versus non-migraine becomes of little bearing in decisions for therapy. Children who fit clearly into a diagnosis of migraine are often more responsive to medication, especially to triptans. Chronic daily headache (CDH) is often dismissed as simple somatization, but population studies show that most patients with CDH evolved from a more intermittent headache pattern, and thus may represent migraine gone awry. Many of these patients have a very

satisfying response to anti-migraine medication.

Nonmedical Interventions

The importance of treatment without pills cannot be overemphasized. Patient and parental reassurance decreases headache severity and frequency in many patients. Demystification of the problem is essential. Many parents think children “shouldn’t have headaches”, and are relieved to hear that childhood headaches occur commonly. Always ask the patient to start a diary of headaches, indicating time of onset, severity, associated symptoms, medication dose and timing, and any possible contributing factors. The diary helps both the provider and the patients to assess the true severity of the headaches, to identify potential lifestyle and dietary triggers, and to assess response to medication. Give the patient strategies that allow them some control over their headaches. Regular meals and routine sleep hours will help. Both oversleeping and lack of sleep contribute to headache. Point out areas that increase stress, such as family strife, school difficulties and extra-curricular activities. Families often minimize the impact of these issues until a physician demands

closer scrutiny. Offer appropriate consultation if warranted.

Eliminate identifiable triggers. Common dietary triggers include caffeine, alcohol, nicotine, tyramine, nitrates, ice cream, and MSG. Many medications provoke headaches. The most common offenders in my practice are oral contraceptives and stimulants, especially methylphenidate. Also beware of the syndrome of analgesic overuse. Many patients with chronic daily headaches have unwittingly precipitated this condition by frequent self-administration of analgesics. NSAIDs are the most frequent causative agent, but overuse of triptans can also precipitate withdrawal headaches. Discontinuing the analgesic will acutely worsen the headache, but ultimately fixes the problem.

Often these measures will be adequate and new medication will not be necessary. Most patients will still have occasional headaches, but because they understand the problem, they manage well with over the counter medications.

Medications take two forms in the treatment of chronic headaches: symptomatic or prophylactic. Table 2 describes common symptomatic

medications, and Table 3 covers prophylaxis. The data are adapted from the AAN Evidence-Based Guidelines for Migraine Headaches, available online at www.aan.com. Most of these data are from studies in adults, extrapolated to children due to lack of data. **KEY:** Letter grades refer to study design: A = multiple well-designed trials with consistent findings. B = some data but inconsistent/suboptimal studies. C = US headache consortium reached consensus in absence of data from randomized trials. “Plus” scale refers to overall efficacy, taking account both statistically significant studies and clinical impression of efficacy by committee consensus: + = either not statistically or not clinically significant; ++ = statistical efficacy, but minimal clinical effect; +++ = statistical efficacy and strong clinical effect.

An individual patient’s response is unpredictable, and often they must try several medications to find the right combination. Be sure that the dose is appropriate for the patient’s age and size; underdosing is a frequent explanation for failure of first line medications such as acetaminophen and NSAID’s. Stress to patients that taking medication early in the course of the

Criterion	Migraine without aura (common migraine)	Migraine with aura (classic migraine)
Minimum # of attacks	5	2
Duration	4 to 72 hours	(none specified)
Characteristics of pain or of aura (requires 2 of 4)	Unilateral Pulsating Moderate or severe Aggravated by activity	—One or more fully reversible neurologic symptoms indicating cerebral or brainstem dysfunction -Gradual onset or several sx in succession -no aura symptom lasting >60 minutes -Headache before or within 60 minutes after aura
Concomitant features	Nausea &/or vomiting Photophobia or phonophobia	Not required

headache increases the likelihood of response. Placebo response is fortunately high.

Tips on abortive migraine therapy:

1. Choose an agent appropriate to severity of headache:

Mild to moderate: Acetaminophen, NSAID's, Midrin, sparing use of Cafergot

Moderate to severe: triptans, ergotamine, SC/nasal DHE, sparing use of Fioricet or opiates

2. Intractable severe headaches require escalation, often parenteral meds:

Ketorolac, IM or IV metoclopramide, IV DHE, sparing use of opioids

3. Considerations when alternatives fail: steroids, ? intranasal Lidocaine

Tips on prophylaxis:

1. When migraines are frequent and/or severe enough to impact quality of life, start prophylaxis.

2. Start low, titrate frequently but slowly and give an adequate trial to see response.

3. Avoid overuse of other meds (i.e frequent abortive therapy)

4. Educate your patient to stress compliance and realistic expectations.

5. Monitor response with a headache diary.

6. Duration is finite—plan to taper if headaches improve for 6 to 12 months

7. Consider perimenstrual prophylaxis if onset of migraine is predictable. Cafergot has proven efficacy for this role; anecdotally Midrin may also work.

8. When choosing medications, consider comorbidity. Athletes often do not tolerate beta-blockers and tricyclics. If the patient has comorbid depression, an SSRI is a better choice than tricyclics.

migraine relief in adolescents. Int'l J. of Clinical Practice 54(7):466-9 Sep 2000.

Ibid, Treatment of childhood headache with DHEM. Headache Nov/Dec 1994 p. 578-580.

Silberstein, S. et al. Management of migraine: An Algorithmic approach. Neurology 55(9 supp 2):S46-52. 2000.

Turk, WR. Childhood Migraine Advances in Pediatrics 47: 161-97 2000.

References

Diamond, S. Migraine Headaches Medical Clinics of N America 75(3): 545-565, May 1991.

Linder, S. Subcutaneous Sumatriptan in the clinical setting. Headache July/Aug 1996 p. 419-422.

Linder, S, & AJ Dawson. Zolmitriptan provides effective



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Childhood Acute Lymphocytic Leukemia

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Childhood acute lymphocytic leukemia (ALL) is one of modern medicine's greatest success stories. Its treatment has served as a model for approaches to other pediatric and adult malignancies and even other diseases. What was a uniformly fatal illness 40 years ago now has an overall cure rate of 75%, with some risk groups approaching 90% long-term survival (Figure 1).

Epidemiology

ALL is the most common malignancy in children, accounting for about one third of pediatric cancer cases, and its incidence is increasing. It is diagnosed in about 2500 children every year in the US. Childhood ALL is more common in boys than girls (1.2:1) and in whites than blacks (1.8:1), and most often develops at between 2 and 5 years of

age

Genetics

ALL is associated with both heritable and specific chromosome abnormalities. Constitutional chromosomal abnormalities and fragility syndromes associated with increased risk of childhood leukemia include trisomy 21, Bloom syndrome, Fanconi's anemia, ataxia-telangiectasia, neurofibromatosis, Schwachman syndrome, and, rarely, Klinefelter's syndrome. Siblings of children with leukemia are two to four times more likely to develop the disease than the general population, and family and sibling aggregates have been reported. The monozygotic twin concordance rate is 25% in the first year after the affected twin is diagnosed, dropping to baseline if the unaffected twin reaches age 7 without developing ALL. Reproducible connections between environmental factors and childhood leukemia have not been shown, however. Exceptions are clear associations with exposure to therapeutic and other forms of ionizing radiation and certain toxic chemicals, such as benzene and some chemotherapeutic agents. A recent cooperative group trial found

especially lymphoma and Kaposi's sarcoma. Children with immunodeficiency syndromes, such as Wiskott-Aldrich syndrome, congenital hypo- or agammaglobulinemia, and ataxia-telangiectasia, have elevated rates of lymphoma. Specific connections between childhood ALL and exposure to other viruses, prenatally as well as after birth, have not been established.

Molecular Pathogenesis

ALL develops through clonal expansion when a single lymphoid cell undergoes malignant transformation and replicates endlessly. Most cases of childhood ALL are from the transformation and clonal expansion of different stages of B or T cell maturation. Research on the process of malignant transformation in ALL has shown that genes involved in cell cycle control (p53, p16, and the MYC gene), apoptosis (bcl-2) and cell differentiation are frequently found to be involved in the cytogenetic abnormalities found in leukemic cells. Genes involved with childhood ALL include:

Precursor B cell ALL: t(9;22) (Philadelphia chromosome), 11q23 and 19p13

T cell ALL: 14q11, 7q34-35

Mature B-cell ALL (Burkitt's Leukemia): 8q24, 14q32, 22q11

The presence or absence of cytogenetic abnormalities impacts prognosis. The Philadelphia chromosome, t(9;22) and rearrangements involving 11q23 portend a very poor prognosis. Trisomies 4 & 10 are common and are associated with an excellent prognosis. Along with the cytogenetics, the DNA index is an important prognostic factor. Leukemia cells with >56 chromosomes (DNA >1.16) have a better prognosis. DNA indexes of 1 or less (< 48 chromosomes) is a negative prognostic feature.

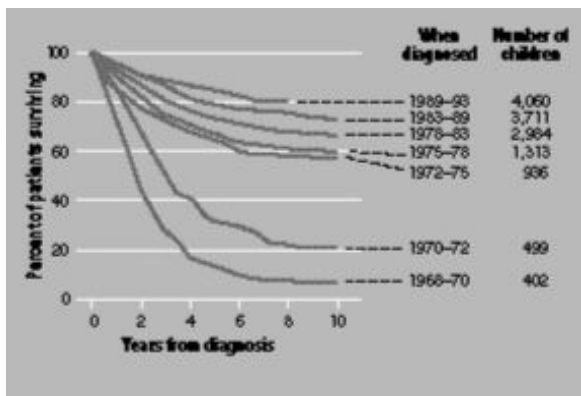


Figure 1. ALL survival in children treated at various time periods starting in the 1960s.

no increased risk of leukemia caused by exposure to electromagnetic fields. Viral infections and immunodeficiency syndromes are also implicated in development of cancer. Epstein-Barr virus is seen in Burkitt's lymphoma/leukemia. HIV infection is associated with malignancy,

Pathology

Lymphoblasts classically have been identified according to the French-American-British (FAB) system. They are designated L1 (84% of cases), L2 (15% of cases) or L3 (1%-same appearance as Burkitt's lymphoma cells) on the basis of light microscopic features, including size of the cell and nuclear-to-cytoplasm ratio. This system is no longer useful as a prognostic indicator and has been replaced. Current leukemia diagnosis is based on the different and aberrant cell surface marker expression of leukemia cells when compared to normal. Using flow cytometry, cell surface marker expression on individual cells is determined by monoclonal antibodies. Immunobiology has greatly increased the ability to characterize and separate the different types of leukemias as well as subgroups in ALL.

Clinical Presentation and Differential Diagnosis

Presenting complaints in ALL may be quite nonspecific and subtle. More often than not, they represent the bone marrow failure secondary to leukemic infiltration. The child may have thrombocytopenia (petechiae, purpura and bleeding), neutropenia (fever or infections) or anemia (fatigue, pallor, exercise or congestive heart failure) Table 1 lists common findings at diagnosis.

Parents or physicians may mistake bone pain, caused by rapid expansion of leukemic cells within the marrow space, for growing pains. Eventually, the pain progresses enough to cause a limp or frank refusal to

bear weight. Nonspecific symptoms, such as anorexia, arthralgias, lymphadenopathy, chronic cough, or simply "looking ill," may also prompt an office visit. The child with ALL may have swollen glands and an enlarged liver and spleen. Hard, non-mobile, non-tender, matted lymph nodes should immediately raise the specter of malignancy, while mobile, tender, firm, or fluctuant nodes are more likely to represent infection. Patients with T-cell disease, particularly adolescents, may present with superior vena cava syndrome, which is suggested by persistent cough, facial swelling, and orthopnea. Central nervous system involvement, while rare at initial diagnosis, may lead to headache, nausea, vomiting, stiff neck, or other signs of increased intracranial pressure.

The differential diagnosis of leukemia includes infection, rheumatologic processes, and other hematologic diseases. Epstein-Barr virus, cytomegalovirus, and other viral illnesses such as pertussis and parapertussis are all good mimics of

ALL. Rheumatologic disease is often difficult to differentiate from ALL, especially when blood counts are normal. Presentations of ALL also are similar to those of hematologic disorders causing cytopenias, including idiopathic or immune thrombocytopenic purpura (ITP), aplastic anemia, transient erythroblastopenia of childhood, and neutropenia. ITP deserves special comment because pediatricians see it so often. Acute onset of severe, isolated thrombocytopenia in an otherwise healthy child without hepatosplenomegaly or adenopathy is unlikely to be ALL. A review of more than 2,000 cases by the Pediatric Oncology Group revealed no cases of acute leukemia signaled solely by a low platelet count. Although ITP may be diagnosed under these clinical conditions, it is prudent not to administer corticosteroids without a bone marrow examination, except in consultation with a pediatric hematologist. Other pediatric malignancies that can involve the bone marrow may have the same signs and symptoms

Findings at Diagnosis	Patients affected (%)
Hepatosplenomegaly	68
Splenomegaly	63
Fever	61
Lymphadenopathy	50
Petechiae or purpura, easy bruising or	
Mucous membrane bleeding	48
Bone pain	23
White Blood Cell count (ul)	
<10,000	53
10,000-49,000	30
>50,000	17
Hemoglobin (g/dl)	
<7.0	43
7.0-11.0	45
>11.0	12
Platelet count (uL)	
<20,000	28
20,000-99,999	47
>100,000	25

as ALL. These diseases include neuroblastoma, non-Hodgkin's lymphoma, rhabdomyosarcoma, and rarely, retinoblastoma. The physical exam and laboratory analysis generally narrows the possibilities quickly.

Diagnosis

A routine complete blood count (CBC) with differential and smear examination is a good place to start for any child whose symptoms suggest hematologic abnormalities.

A chemistry panel, including uric acid and lactate dehydrogenase, is a necessity. While these metabolic indicators can be normal early in the disease, they may reveal incipient tumor lysis syndrome and signal the need for urgent medical intervention. Tumor lysis usually develops after chemotherapy has begun to destroy cells, but it can occur in untreated patients with rapidly evolving disease, particularly those with mature B cell or T cell ALL or any patient with high white blood cell counts ($>100,000$). Uric acid, which accumulates as the DNA of the lymphoblasts is broken down, may precipitate in renal tubules. Lymphoblasts are very metabolically active and contain large amounts of potassium and phosphorus. Rapid cell death can lead to hyperkalemia, hyper- or hypocalcemia, hyperphosphatemia, and abnormalities of renal function, including fulminant renal failure. Tumor cell lysis is a true medical emergency that can progress quickly to multisystem organ failure and death. A chest X-ray should be performed early when you suspect ALL. Only 5% to 10% of patients have a mediastinal mass at presentation, usually associated with T-cell leukemia, but the existence of a mass, its location, and the degree of associated tracheal compression signal the need for urgent diagnosis and therapy. Do not administer corticosteroids to any child you

suspect has leukemia until after the bone marrow examination has been done. Leukemic cells are extremely sensitive to all forms of prednisone, and even small doses, such as a five-day burst for an asthma exacerbation or a short course for pharyngeal swelling associated with presumed infectious mononucleosis, may partially treat an evolving leukemia. There is a danger that this partial treatment will mask the diagnosis or even cause tumor lysis syndrome.

A bone marrow aspirate/biopsy is performed to obtain the necessary samples to fully characterize the leukemia. Staging of ALL requires examination of lumbar cerebrospinal fluid. CNS leukemia is defined as five or more white blood cells/ μL with blast cells seen on centrifuged preparation.

Pediatricians' role in the diagnosis

After discussing the case with your referring oncologist, you need to discuss your suspicions with parents and patients. Tell parents that their son or daughter may have a potentially serious disease and that identifying it is critically important to the child's prognosis. Mention leukemia as one possibility, so that being referred to a cancer center does not take the family by surprise. Stress that all of the possible diagnoses are treatable and that many are often fully curable. Offering them hope will help them confront the challenges that lie ahead.

Some parents are able to formulate questions about the disease soon after learning of the possible diagnosis. The most common queries and appropriate answers are:

Q: What caused my child's illness?

A: We don't know, but it's not something you or your child did or did not do, or could control.

Q: Was it caught in time?

A: Yes, even advanced leukemia is potentially curable, though treatment may be somewhat different than in cases caught early.

Q: How long has my child been ill without our knowing it?

A: Three to six months at most.

What you tell the child depends, of course, on her age and developmental stage. Even very young children eventually know quite a lot about their disease. At referral, the child needs to know that she has something serious that requires treatment, that she did nothing to cause the illness, and that someone will tell her exactly what will happen at each step of the way. Most tertiary care centers use conscious sedation for many procedures, and they place central venous catheters early to avoid painful needle sticks. Many children older than 10 are worried about dying. If the child voices this concern, tell her that though some people with leukemia do die, most do not, and she is expected to do well. Avoid giving the child more information than she has requested.

References

1. Margolin JF, Poplack DG: Acute lymphoblastic leukemia. In Pizzo PA, Poplack Dg (eds): Principles and Practice of Pediatric Oncology, 3rd ed. Philadelphia, JB Lippincott Company, 1997.
2. Frieberg, SE and Shurin SB. ALL: Diagnosis and Outlook. Contemporary Pediatrics. Feb 1998
3. Frieberg SE and Shurnin SB. ALL: Treatment and Beyond. Contemporary Pediatrics. March

1998

4. Dubansky AS et al. Isolated thrombocytopenia in children with ALL: A rare event in a Pediatric Oncology Group Study. *Pediatrics* 1989; 84(6): 1068-1072.

5. Pui CH. Acute lymphoblastic leukemia. *Pediatric Clinics of North America*. 1997; 44(4): 831-842.

Part 2 - Continuation of Treatment to follow in October
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Computers and the Internet – An Overview

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Introduction

Computers today are faster, smaller, and cheaper than ever. Many of us now use a pager, cell phone, personal data assistant, laptop and desktop computer all before many Americans eat breakfast. Technology has become so enmeshed in our daily lives that it is difficult to envision life without these 21st century tools. We are becoming overrun with acronyms such as PDA, SSL, dpi, and SDRAM faster than you can say gigahertz (GHz) or megabyte (MB). In this article, I intend to provide you with a brief overview of the history of internet, define some often misunderstood computer terminology, and finally provide some information and links so that the anti-Luddites among you can appease that thirst for enlighten-

ment.

The Internet

The Internet is first conceived in the early '60s. Under the leadership of the Department of Defense's Advanced Research Project Agency (ARPA), it grows from a paper architecture into a small network (ARPANET) intended to promote the sharing of super-computers amongst researchers in the United States. The ARPANET is a success from the very beginning. Although originally designed to allow scientists to share data and access remote computers, email quickly becomes the most popular application. The ARPANET becomes a high-speed digital post office as people use it to collaborate on research projects and discuss topics of various interests. The original ARPANET computers, called *nodes*, were located at UCLA, Stanford, the University of California-Santa Barbara, and the University of Utah.

By 1971, there were 15 nodes on the ARPANET. The first computer-to-computer *chat* happened at UCLA in 1972. A chat was a real-time written conversation between users at separated computers. In 1973, the ARPANET went international, with connections to University College in London, England, and the Royal Radar Establishment in Norway. Queen Elizabeth II sent the first royal email in 1976. Over this time, the terms *packet* (small package of data) and *protocol* (the language computers must share to successfully send/receive packets) became common. In 1979, students at Duke University and the University of North Carolina created USENET newsgroups. Users from around the world joined these discussion groups to talk about the net, politics, religion, and thousands of other subjects. By 1981, ARPANET had 213 hosts, and added a new one

about every 20 days. In 1982, ARPA introduced a new set of protocols, the Transmission Control Protocol (TCP) and Internet Protocol (IP), commonly known as *TCP/IP*, for ARPANET. This system gave each computer in the network a unique number, to make it easier to talk directly to the one you want.

The mid-80s marked a boom in the personal computer and super-minicomputer

industries. By 1983 computers had shrunk from room-sized to desktop. In 1984, the number of nodes was well over 1000, and the concept of *Domain Name Systems (DNS)* to identify each node is developed. This made life much easier. Instead of 8-10 digit numbers to remember for each of the 1000 computers, now you could assign them an actual name, such as computer_one@UCLA.net, computer_two@UCLA.net, etc. Packets then were directed to the domain name *server* (master computer at UCLA, e.g.), which would then translate into the corresponding IP number via a database. This made it much easier for people to access other servers, because they no longer had to remember numbers. Also in 1984, William Gibson coined the term "cyberspace" in his novel "Neuromancer."

In 1986, a new network, NSFNet (via the National Science Foundation), was created, with higher speed cables. By 1987, there were over 10,000 computers in the network, now called *hosts*. Sen. Al Gore introduced a concept and plan for a national US research and education network, which would take 4 years to finally come to fruition. In 1990, the ARPANET was shut down, and the NSFNet was up to 100,000 hosts under at least 10,000 domain names in over 30 countries. The term *Internet* was

born around then. Computers were exchanging over 3 billion data packets per month. The World.com broke ground in 1990 as the first commercial dial-up Internet access provider, and was soon followed by Compuserve and MCI. In 1990, the US Supreme Court began publishing their decisions on the Internet, and a man connected a toaster to the Internet and became the first to remotely control another machine via the Net in history. This landmark year was ultimately highlighted by the coining of the term “World Wide Web (WWW)” by a scientist from Switzerland named Tim Berners-Lee.

Over the next two years, the Internet expanded dramatically, and connected greater than one million hosts over 17,000 networks in 33 countries, sending over 1 trillion data packets per month. Computers of all types and operating systems were trying to talk to communicate. In order to achieve some form of standardization, *browsers* were created. These programs let the user look at the information on the Internet, regardless of the operating system of the computer that stores that information. A programmer at the University of Minnesota created the first browser, nicknamed “Gopher”. 1993 was a notable year

for the Internet. The creation of the graphics-based “Mosaic” browser introduced the world to the potential of the Internet. It was now possible to combine words, pictures and sounds on web pages, and was nearly as easy as using a word processor. The Swiss research institute CERN announced its decision not to patent or claim any copyright fees for WWW technology. America Online was introduced in February 1993, and President Clinton and Vice President Gore went online as well.

While many doubted the staying power of the Internet up until this time, by 1994 the Internet and the World Wide Web clearly were going to last. There were more than 3 million hosts in over 50 countries. Businesses and media began taking notice of the Internet. Pizza Hut made it possible to order online and First Virtual became the first cyber-bank. The Rolling Stones broadcast their Voodoo Lounge tour on the Internet, and the Vatican went online with www.vatican.va. The first WWW conference took place at CERN, and, ridiculously overcrowded, was dubbed the “Woodstock of the Web.” In 1995, the Net is at the forefront of society. *Search engines* such as Lycos, Alta Vista, and Deja Net become hits. These programs

targeted information from among the vast resources based on key words or other content. Internet companies launch IPOs on the stock market left and right. Also in 1995, Sen. Jim Exon proposed the Communications Decency Act, which represented the first attempt at censorship. In January 1996, there were 100,000 web sites, and by June that number had climbed to 230,000. The term *hacking* was publicized after the US Dept of Justice website was defaced. By 1997, over 190 billion emails were sent annually. For many, the Monica Lewinsky affair became the most important event on the Net in 1998. The Internet demonstrated its full potential as a publishing medium, and for the first time, it was clear that the WWW is not a toy for nerds but has instead become an effective mass medium. In January of 1998, Matt Drudge published early reports of Bill Clinton’s adventures with a White House intern at his gossip site, The Drudge Report, and set off a tidal wave of journalistic furor, culminating with the impeachment of the president at the end of the year. The live broadcast of a birth on the “Health Network” was not only viewed by over a million visitors, but also aroused interest in the offline world.